UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/782,721	02/12/2001	H. Michael Shepard	126745200402	5394

22836 7590 03/01/2004

BAKER & MCKENZIE
660 HANSEN WAY
PALO ALTO, CA 94304

EXAMINER	
CRANE, LAWRENCE E	

ART UNIT	PAPER NUMBER
1623	

DATE MAILED: 03/01/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/782,721	SHEPARD ET AL.	
	Examiner	Art Unit	
	L. E. Crane	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11/10/03(amdtD)*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *56-89* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *56-89* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *11/10/03*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

No claim has been cancelled, claims **56-59, 62 and 76** have been amended, and no new claims have been added as per the amendment filed November 10, 2003. A sixth Information Disclosure Statement (IDS) filed November 10, 2003 has been received with one cited reference and made of record.

The copy of claims provided alleged a claim **89** but no claim **89** was found at the end of the claims provided. A copy of claim **89** from an earlier set of claims was examined in lieu of the noted missing claim.

Claims **56-89** remain in the case.

Claims **58, 62 and 76** are objected to because of the following informalities:

In claim **58** at line 9, the term "compound" is grammatically incorrect. Did applicant intend the term to read -- substituent --?

In claim **76** the structure of the defined substituent includes a terminal CH_2 group as part of a vertically drawn " -NH-C(=O)-CH_2 " which appears to represent a valence error. Did applicant intend it to read -- -NH-C(=O)-CH_3 --? See also claim **62** at line 22 where the same structure and the identical error also appears.

Appropriate correction is required.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not deemed to be persuasive.

Applicant noted the objection and suggested the correction thereof, but has failed to amend either claim **62 or 76** in the manner suggested or in any other manner.

Claim **85** is rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

In claim **85** reference is made to assays using compounds which have been disclosed generically or subgenerically. This reference to compounds is lacking support from a proper

written description in light of the disclosure (p. 60) wherein no examples have been described which disclose the successfully testing of any single compound.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has noted the rejection but has not responded in any other manner. Therefore, the rejection has been maintained.

Claims **56 and 57** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims **56 and 57** are directed to methods of inhibiting and treating wherein the particular disease to be treated has not been specified, the particular active ingredients have not been defined, and the host has not been defined by the functional terms "phosphoramidatyl prodrug" and "hyperproliferative cell(s)." These terms are the equivalent of laundry list disclosures which fail to meet the written description requirement because each, taken individually or taken together, "... would not 'reasonably lead' those skilled in the art to any particular species." (MPEP §2163 (A) at p. 2100-160, column 2, making reference to *In re Rushig*, 379 F2d 990, 995 (CCPA 1967).

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has noted the instant grounds of rejection, but the amendments made to the instant noted claims do not overcome the rejection because the "laundry list" problems noted in the rejection have not been effectively addressed by the amendments newly entered.

Claims **56-61, 81-84 and 86-89** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims as defined by the terms "hyperproliferative cell(s)" is excessively broad because said term reads on multiple different disease conditions including all varieties of neoplasms (cancers cells), psoriasis, and infections caused by rapidly dividing microorganisms (SARS, Ebola,.Marburg, Flesh eating bacteria, etc.). Only in claim **89** is the term limited to specific neoplastic diseases.

B. The nature of the invention as described in the specific examples is limited to a showing that a single compound, a phosphoramidated derivative of 5-bromovinylated 2'-deoxyuridine nucleoside is much more effective that the non-phosphoramidated BVDU base compound in treating certain specific neoplastic diseases, human breast carcinoma and human colon carcinoma in particular.

C. The state of the prior art; the extensive prior art of record, as presently understood and reviewed, does not anticipate or render obvious the treatment of carcinomas with a phosphoramidated BVDU.

D. The level of one of ordinary skill is defined by the need to understand organic synthesis, and the testing of compounds in *in vitro* cell culture.

E. The level of predictability in the art is low because only two closely related neoplastic disease conditions have been shown to be effectively inhibited by a phosphoramidated BVDU compound.

F. The amount of direction provided by the inventor is limited to showing how to make and administer a single phosphoramidated BVDU compound to cause inhibition of two closely related neoplastic disease conditions.

G. The existence of working examples is limited to a single compound administered to cells in in vitro culture infected by two closely related carcinomas.

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive because the disclosure does not to described how to effectively treat anything other than carcinoma in humans breast and colon tissue.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant's arguments are noted but do not include any additional experimental data showing how to administer additional compounds to treat the carcinomas already of record, and/or data disclosing the effective treatment of additional neoplastic disease conditions included within the scope of applicant's claims. Additional data of this kind should be submitted in the form of a declaration under 37 C.F.R. §1.132 and would provide a proper basis for a less restrictive analysis of applicant's claims.

Claims **62-80** are rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one of ordinary skill in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The fundamental issue here is whether practicing the full scope of the instant invention is possible without undue experimentation. As provided for in In re Wands (858 F.2d 731, 737; 8 USPQ 2d 1400, 1404 (Fed Cir. 1988) the minimum factors to be considered in determination of whether a conclusion of "undue experimentation" is appropriate are as follows:

A. The breadth of the claims is very large particularly in view of terms found in claim **62** wherein a large array of compounds is disclosed, only one of which is actually prepared and shown to be thymidylate-synthase activatable in a testing protocol.

B. The nature of the invention is compounds and methods of treating neoplastic disease conditions and a related protocol for determination of the anti-neoplastic activity of test compounds

C. The state of the prior art is not well advanced as revealed by the absence of an art rejection.

D. The level of one of ordinary skill is high, a knowledge of chemical synthesis, biochemistry, enzymology and pharmacology being required to carry out all elements of the instant claimed invention.

E. The level of predictability in the art is low, because of the very small amount of testing data.

F. The amount of direction provided by the inventor is very low because only a single compound, the 5'-phosphoramidate ester of 5-bromovinyluridine has been synthesized and shown to have the anti-neoplastic activity.

G. The existence of working examples is very limited: only a single compound has been prepared and shown to have anti-neoplastic activity; and

H. The quantity of experimentation needed to make or use the invention based on the content of the disclosure would be excessive, particularly because only a single compound has been prepared and its preparation has been shown to be very sensitive to reaction conditions, a showing that provides no basis for extrapolation to other compounds with different toxophoric substituents as provided for by the instant claims.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant's arguments are noted but do not include any additional experimental data showing how to make other compounds included within the scope of applicant's claims. Additional data of this kind should be submitted in the form of a declaration under 37 C.F.R. §1.132 and would provide a proper basis for a less restrictive analysis of applicant's claims.

Claims **56-59, 61-63, 65, 72 and 81-87** are rejected under 35 U.S.C. §112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

In claims **56 and 57** the term "a 5'-phosphoryl or phosphoramidatyl prodrug of a 5-substituted pyrimidine nucleoside or nucleotide, a derivative or a metabolite thereof" fails to completely define the structural metes and bounds of the included terms "phosphoramidatyl," "5-substituted pyrimidine nucleoside or nucleotide," and "a derivative or a metabolite thereof."

In light of the initial requirement of a "5'-phosphoryl or phosphoramidatyl" substituent it is also unclear where the additional "phosphate" group(s) are located as required by the included term "nucleotide." See also claim **58** wherein the terms "prodrug," "derivative," and "metabolite" also appear at lines 1-2.

Applicant's arguments with respect to claims **56-58** have been considered but are deemed to be moot in view of the new grounds of rejection which has been necessitated by applicant's amendment of the noted claims.

In claim **57** at line 1, the term, "hyperproliferative cells, " is indefinite for failure to specify the particular disease being referred to; is it cancer and if so which cancer or cancers? Or alternatively, is the disease some variety of psoriasis? Ebola? Marburg? A flesh eating bacterial infection? See also claims **56, 58, 81-84, 86 and 87**. The term "pathological hyperproliferative cell" is no better because it also fails to define the particular disease(s) to be treated.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant notes the instant grounds of rejection and the argues generically that the instant claims "employ language conventionally used in the art to which the invention pertains and therefore adequately define the metes and bounds of the claimed invention," but otherwise does not respond to the individual grounds of rejection. Examiner deems this to be non-responsive.

In claim **58** the terms "an electrophilic leaving group" (line 4), "a phosphoryl or phosphoramidatyl" (line 6), and "masked phosphoryl," (line 9) are incomplete for failure to completely specify the metes and bounds of the chemical structures being claimed.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant notes the instant grounds of rejection and the argues generically that the instant claims "employ language conventionally used in the art to which the invention pertains and therefore adequately define the metes and bounds of the claimed invention," but otherwise

does not respond to the individual grounds of rejection. Examiner deems this to be non-responsive.

In claim **58** the terms "sugar," "thio sugar," "carbocyclic," "acyclic analogs and derivatives of a sugar," "a thio-sugar or a carbocyclic," "derivatives," "analogs" are indefinite for failure to provide the structural details to the chemical species being referred to. In addition, the term "carbocyclic" is unnecessarily repeated and also is not further provided with an upper size limit; the terms "sugar" and "thiosugar" are compounds (-- sugar group --?); and, the terms "analogs" and "derivatives" are open ended (no metes and bounds or other limits on the definition).

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant notes the instant grounds of rejection and the argues generically that the instant claims "employ language conventionally used in the art to which the invention pertains and therefore adequately define the metes and bounds of the claimed invention," but otherwise does not respond to the individual grounds of rejection. Examiner deems this to be non-responsive.

Claim **59** is indefinite for failure to provide the structural details for the chemical species ("masked phosphoryl moiety" and "phosphoramidatyl moiety") being referred to.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant notes the instant grounds of rejection and the argues generically that the instant claims "employ language conventionally used in the art to which the invention pertains and therefore adequately define the metes and bounds of the claimed invention," but otherwise does not respond to the individual grounds of rejection. Examiner deems this to be non-responsive.

In claim **62** at lines 10-11, the term "aromatic hydrocarbyl" is incomplete because it is not clear whether applicant is referring to an
-- aromatic hydrocarbyl group -- or a compound. The same criticism also applies to the term "a heteroaromatic." Also said terms both lack an upper size limit and therefore render the

instant compound indefinite for failure to provide adequately defined structural metes and bounds. Also, the term "heteroaromatic" is incompletely defined for failure to define the identity or limits on the proportion of the heteroatom or heteroatoms present.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant notes the instant grounds of rejection and the argues generically that the instant claims "employ language conventionally used in the art to which the invention pertains and therefore adequately define the metes and bounds of the claimed invention," but otherwise does not respond to the individual grounds of rejection. Examiner deems this to be non-responsive.

The non-statutory double patenting rejection, whether of the obviousness-type or non-obviousness-type, is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent. *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969); *In re Vogel,* 422 F.2d 438, 164 USPQ 619 (CCPA 1970); *In re Van Ornam,* 686 F. 2d 937, 214 USPQ 761 (CCPA 1982); *In re Longi,* 759 F.2d 887, 225 USPQ 645 (Fed. Cir 1985); and *In re Goodman,* 29 USPQ 2d 2010 (Fed. Cir. 1993).

A timely filed terminal disclaimer in compliance with 37 C.F.R. § 1.321(b) and (c) may be used to overcome an actual or provisional rejection based on a non-statutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 C.F.R. §1.78(d).

Effective January 1, 1994, a registered attorney or agent or record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 C.F.R. §3.73(b).

Claims **56-61, 81-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim **1-12** of U. S. Patent No. **6,495,553**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **62-80** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **36-39** of U. S. Patent No. **6,339,151**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-7** of U. S. Patent No. **6,245,750**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-30** of co-pending Application No. **10/119,927**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant has acknowledged but has deferred response to this grounds of rejection.

Claims **56-61 and 81-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-22** of co-pending Application No. **10/051,320** (for the PG PUBS version, see PTO-892 ref. **P3**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Applicant's arguments with respect to claims **56-61 and 81-89** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **62-80** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1 and 53-83** of co-pending Application No. **10/681,418**. Although the conflicting claims are not identical, they are not patentably distinct from each other because the method of treatment and the alleged active ingredients are directed to substantially overlapping subject matter.

Applicant's arguments filed November 10, 2003 have been fully considered but they are not persuasive.

Applicant's arguments with respect to claims **62-80** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **56-84 and 86-89** are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims **1-10** of U. S. Patent No. **6,683,061** (PTO-892 ref. **AB**). Although the conflicting claims are not identical, they are not patentably distinct from each other because the compounds and the methods of treatment are overlapping with the instant claimed subject matter.

Applicant's arguments with respect to claims **56-84 and 86-89** have been considered but are deemed to be moot in view of the new grounds of rejection.

Claims **56-84 and 86-89** of this application conflict with claims **1-30** of co-pending Application No. **10/119,927** claims **1-22** of co-pending Application No. **10/051,320** and claims **1 and 53-83** of co-pending Application No. **10/681,418**. 37 C.F.R. §1.78(b) provides that when two or more applications filed by the same applicant contain conflicting claims, elimination of such claims from all but one application may be required in the absence of good and sufficient reason for their retention during pendency in more than one application. Applicant is required to either cancel the conflicting claims from all but one application or maintain a clear line of demarcation between the applications. See MPEP §822.

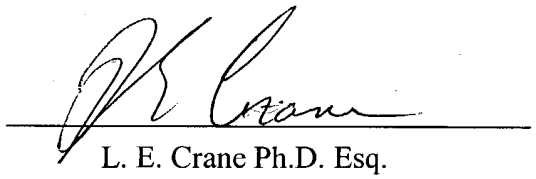
Papers related to this application may be submitted to Group 1600 via facsimile transmission(FAX). The transmission of such papers must conform with the notice published in the Official Gazette (1096 OG 30, November 15, 1989). The telephone number to FAX directly to Examiner's computer is 571-273-0651. Telephone numbers for alternative FAX machines operated by Group 1600 are **presently unavailable**.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner L. E. Crane whose telephone number is **571-272-0651**. The examiner can normally be reached between 9:30 AM and 5:00 PM, Monday through Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson, can be reached at **571-272-0661**.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is **571-272-1600**.

LECrane:lec
02/25/2004



L. E. Crane Ph.D. Esq.
Patent Examiner
Technology Center 1600